REMARKS

Claims 1-21 are pending in this application. Claims 5-9, 11-15, 17, 18 and 20 are hereby cancelled without prejudice to pursuing these claims in a continuing application. Claims 1, 10 and 19 are hereby amended. Upon entry of these amendments, claims 1-4, 10, 16, 19 and 21 are pending and under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

Applicant amends claim 1 to substitute the term "comprising" for the phrase "in contact with" and to substitute the phrase "the development of atrioventricular septal defects" for the phrase "effects associated with congenital heart disease." Support for amended claim 1 may be found throughout the application as filed with exemplary support at paragraphs [0002], [0070] and [0071]. Applicant amends claim 10 to substitute the term "identifying" for the term "isolating". Applicant amends claim 19 to recite a screening method in which the measuring step need not be performed *in vivo*. Support for amended claim 19 may be found throughout the application as filed with exemplary support at paragraph [0071]. Accordingly, Applicant respectfully submits that no new matter has been added.

I. **Patentability Arguments**

A. The Written Description Rejections Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn.

Claims 8, 9, 19 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor at the time of filing had possession of the claimed invention. Specifically, the Examiner alleges (on page 3 of the Office Action) that the detected modulator is not particularly limited by its structure or mode of action.

Applicant cancels claims 8, 9 and 20. Applicant respectfully submits that the subject matter of claim 19 as currently amended is a screening method for the identification of a modulator of the development of atrioventricular septal defects (AVSDs) and not a modulator itself and is adequately supported by the specification. The specification teaches that 65% of

transgenic mouse embryos comprising a heterozygous disruption of the CCN1 gene possess AVSDs of varying severity. *See* paragraph [0071]. Further, the specification describes methods, including histological analysis and Doppler echocardiography, for detecting atrioventricular septal defects in the transgenic mouse embryo or in postnatal mice arising therefrom. *See*, e.g., Figure 2 and paragraph [0009]. Finally, the specification teaches the phenotypes associated with AVSDs at paragraph [0033]. Thus, the distinguishing characteristics for identification of a suspected modulator of the development of AVSDs are described by the specification such that one of ordinary skill in the art would know that Applicant was in possession of the screening method at the time of filing the application. Therefore Applicant respectfully submits that the rejection of claims 8, 9, 19 and 20 for lack of written description should be withdrawn.

B. The Enablement Rejections Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn.

Claims 19 and 29 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention. Specifically, the Examiner alleges (on page 5 of the Office Action) that the skilled artisan would not know *a priori* whether the use of a suspected modulator results in altering the phenotype of the $CCN^{+/-}$ mice as compared to the control.

Applicant proceeds with this response under the assumption that Examiner's enablement rejections are directed to claims 19 and 20. Applicant cancels claim 20 and amends claim 19. Claim 19, as amended, covers a screening method wherein the phenotype of transgenic mouse embryos (or of postnatal mice arising therefrom) need be measured only after contacting said embryos with a suspected modulator, obviating the need for *in vivo* testing. As noted supra, the specification teaches that 65% of transgenic mouse embryos comprising a heterozygous disruption of the CCN1 gene possess AVSDs of varying severity by E14.5. *See* paragraph [0071]. To identify a modulator, one of ordinary skill in the art contacts a plurality of said embryos with a suspected modulator and then calculates the percentage of embryos (or of postnatal mice arising therefrom) possessing at least one phenotype associated with an AVSD. The specification teaches that embryonic cultures may be used for the screening of modulators, *see* paragraph [0032], and that histological analysis may be used to measure said phenotypes, *see*, e.g., Figure 2. A modulator increases the percentage of embryos (or of postnatal mice

arising therefrom) possessing at least one AVSD above 65% or decreases said percentage below 65%. Thus, the specification enables one of ordinary skill in the art, without undue experimentation, to determine if a suspected modulator is capable of altering the phenotype of the embryos in question.

In view of the forgoing, Applicant respectfully submits that this amendment overcomes the rejection under 35 U.S.C. § 112, second paragraph, and requests reconsideration and withdrawal thereof.

C. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 1-7 and 10-18 are rejected under 35 U.S.C. § 102(b) as anticipated by Mo *et al.* (Mol Cell Biol, 2002, 22:8709-8720). The Examiner characterizes Mo *et al.* (on page 6 of the Office Action) as "teach[ing] a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome (sic) comprise heterozygous or homozygous disruptions of the CCN1 gene and testing the transgenic mice for their genotype." The Examiner alleges that AVSDs (or predisposition thereto) are inherent in transgenic mice comprising a heterozygous disruption in CCN1.

Applicant cancels claims 5-7, 11-15, 17 and 18.

Claim 1 as currently amended covers a transgenic mouse comprising a suspected modulator of the development of atrioventricular septal defects wherein the genome of said mouse comprises a heterozygous disruption in the CCN1 gene. Mo *et al.* does not disclose the limitation "comprising a suspected modulator of the development of atrioventricular septal defects." Thus, the reference fails to meet all the limitations of claim 1 and cannot anticipate claim 1 or claims 2-4 which depend therefrom under 35 U.S.C. § 102(b). Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejections of claims 1-4 under 35 U.S.C. § 102(b).

Claim 10, as currently amended, covers a method of producing a mouse with an AVSD. Mo *et al.* characterizes transgenic mice comprising homozygous disruptions of the CCN1 gene, yet contains no description of any cardiovascular defects. No attempt is made to characterize transgenic mice comprising heterozygous disruptions of CCN1. Even assuming, *arguendo*, that AVSDs are inherent in the mice disclosed in Mo *et al.*, the instant specification teaches that only 65% of transgenic mice heterozygous for disruptions of the CCN1 gene display an AVSD. Mo

et al. fails to disclose a step wherein said mice are tested for a phenotype associated with an AVSD or a step wherein the subset of said mice displaying said phenotype are identified. Thus, the reference fails to meet all of the limitations of claim 10 and cannot anticipate claim 10 under 35 U.S.C. § 102(b). Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejections of claim 10 under 35 U.S.C. § 102(b).

Claim 16 covers a method of identifying a mouse with an AVSD. As noted supra, Mo *et al.* fails to disclose (1) that transgenic mice heterozygous for disruptions of the CCN1 gene display AVSD or (2) testing of said mice for an AVSD so that mice displaying an AVSD can be identified. Therefore, Applicant respectfully submits that the reference fails to meet any of the limitations of claim 16 and respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

D. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 19 and 20 are rejected under 35 U.S.C. § 103(a) in view of Mo *et al.*, in view of Christensen *et al.* (Am J Ophysiol, 1977, 272:H2513-H2524) and Bruneau *et al.* (Cell, 2001, 106:709-721) as evidenced by Hickey *et al.* (Cytogenet Genome Res, 2003, 100:276-286). Applicant cancels claim 20. The Examiner characterizes Mo *et al.* as teaching "transgenic mice whose genome comprises a heterozygous disruption of the CCN1 gene." After characterizing Mo *et al.*, the Examiner alleges (on page 7 of the Office Action) that the claimed invention differs from the prior art [Mo *et al.*] in the use of said mice in a method of identifying a modulator of symptoms associated with atrioventricular septal defects. The Examiner characterizes Christensen *et al.* as teaching that "mouse models of heart disease may serve to develop appropriate therapeutic strategies for human heart disease." Finally, the Examiner characterizes Bruneau *et al.* as teaching "that heterozygous mice models for congenital heart disease can be used to understand the pathway that leads to the development of the disease." The Examiner looks to Bruneau *et al.* to supply the motivation "to use the mice of Mo *et al.* to screen for potential modulators of atrioventricular septal defects."

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981 (CCPA 1974). Second, there must be a reasonable expectation of success. *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986). Finally, there must be some

suggestion or motivation for one of ordinary skill in the art to modify the reference or to combine the reference teachings. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

Applicant submits that Examiner has failed to establish a *prima facie* case of obviousness because the prior art references cited by the Examiner fail, separately and in combination, to teach or suggest that transgenic mice comprising a heterozygous disruption of the CCN1 gene are prone to AVSDs. One of ordinary skill in the art could not find it obvious to use said mice in a method of testing for a suspected modulator of symptoms associated with an AVSD absent a disclosure that said mice are prone to AVSDs.

In view of the failure of Mo *et al.* alone or in combination with Christensen *et al.* and Bruneau *et al.* to teach or suggest that transgenic mice comprising a heterozygous disruption of the CCN1 gene are prone to AVSDs, Applicant respectfully submits that claim 19 is not obvious in view of Mo *et al.* in view of Christensen *et al.* and Bruneau *et al.* and thus requests reconsideration and withdrawal of the rejection to claim 19 under 35 U.S.C. § 103(a).

Claim 21 is rejected under 35 U.S.C. § 103(a) in view of Mo *et al.*, in view of Mah *et al.* (Genet Test, 1999, 3:157-172) and Ciarleglio *et al.* (J Clin Invest, 2003, 112:1280-1286). The Examiner characterizes Mah *et al.* as teaching genetic testing for cardiac disorders and Ciarleglio *et al.* as teaching the benefits of genetic testing to identify predisposition to genetic disorders. The Examiner argues that motivation to combine the references is provided by Mo *et al.* which Examiner alleges teaches "that disruption of CCN1 function plays a role in the development of atrioventricular septal defects."

Applicant submits that Examiner has failed to establish a *prima facie* case of obviousness because none of the prior art references cited by the Examiner provides a motivation to combine the references. Specifically, contrary to Examiner's assertion, Mo *et al.* does not teach that "CCN1 function plays a role in the development of atrioventricular septal defects." Mo *et al.* contains no description of *any* cardiovascular defect in transgenic mice comprising a homozygous or heterozygous disruption of CCN1.

Further, Mo *et al.* contains no suggestion of a correlation between disruption of CCN1 function and the development of AVSDs. In the absence of such a teaching, one of ordinary skill in the art would not have been motivated to combine the references. In view of the failure of Mo

et al. alone or in combination with Mah *et al.* and Ciarleglio *et al.* to provide such a teaching, Applicant respectfully submits that claim 21 is not obvious in view of Mo *et al.* in view of Mah *et al.* and Ciarleglio *et al.* and thus requests reconsideration and withdrawal of the rejection to this claim under 35 U.S.C. § 103(a).

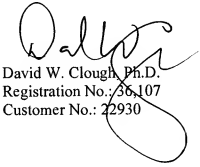
II. **Conclusion**

In view of the foregoing amendments and remarks, Applicant respectfully submits that the claims are now in condition for allowance and early notification thereof is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY LLP

Dated: September 6, 2006

By: 

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